Randomized Controlled Trial to Assess the Impact of High Concentration Intraurethral Lidocaine on Urodynamic Voiding Parameters

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OBJECTIVE To assess whether intraurethral anesthesia decreased voiding efficiency (VE), reduced catheterization pain, and impacted urodynamic parameters in healthy adult females.

METHODS In a randomized, double-blind, placebo-controlled trial, participants received two 5 mL doses of either intraurethral aqueous gel or 4% lidocaine gel. The primary outcome was VE during randomized condition uroflow, defined as voided volume/(voided volume + residual volume). The secondary outcomes were pain during catheterization and to confirm previously reported pressure-flow changes. A sample size of 10 per group was planned to detect a clinically significant decrease in VE with a power ($1\text{-}\beta$) of 0.99.

RESULTS From October to December 2018, 23 women were screened and 18 were randomized to receive placebo ($n = 10$) or lidocaine ($n = 8$). Baseline uroflow VE was similar between the placebo and lidocaine groups ($88 \pm 6.6\%$ vs $91 \pm 5.8\%$, $P = .33$). After study drug administration, the changes in VE (post-pre) were similar between placebo and lidocaine groups ($-5.4 \pm 14\%$ vs $1.7 \pm 6.4\%$, $P = .21$). Visual analog scores were similar following catheterizations (26.7 ± 12.8 mm vs 36.9 ± 26.8 mm, $P = .34$). The lidocaine group exhibited lower average flow rates per voided volume ($0.04 \pm 0.02\ s^{-1}$ vs $0.02 \pm 0.01\ s^{-1}$, $P = .04$).

CONCLUSION Intraurethral administration of 4% lidocaine did not decrease VE compared to placebo and did not change pain scores following catheterization. In the lidocaine group, the average flow rate per voided volume was lower. The decrease in flow rate after local anesthesia to the urethra may indicate that urethral sensory feedback contributes to voiding in human micturition. UROLOGY 133: 72–77, 2019. © 2019 Elsevier Inc.

The lower urinary tract, comprising the bladder, urethra, and external urethral sphincter, is regulated by a complex neural control system to initiate micturition and produce efficient voiding.[1] During normal voiding, the elimination of urine is achieved through detrusor contraction with concomitant relaxation of the external urethral sphincter and urethra.[2] Urine flow through the urethra activates pudendal afferent nerve fibers,[3] which mediate the augmenting reflex to increase the bladder contraction and produce efficient voiding.[4,5] In animals, disruption of urethral sensory feedback either by transection of the sensory branch of the pudendal nerve or administering intraurethral anesthesia reduces voiding efficiency (VE).[6,7] Disruption of this reflex mechanism may also contribute to incomplete voiding and urinary retention in humans.

Shafik et al reported that intraurethral 5% xylocaine gel increased strain-voiding and increased postvoid residual volume (PVR) in healthy adult males and females.[8] In contrast, Kisby et al reported that intraurethral 2% lidocaine did not change VE in healthy adult females; however, participants receiving lidocaine demonstrated an interrupted flow pattern and elevated pelvic floor muscle activity.[9] Interestingly, if the participants with an abnormal baseline uroflowmetry were excluded from the analysis, VE was lower in the intraurethral lidocaine group.[9] In our study, we explored further the role of urethral sensory feedback by increasing the concentration and duration of lidocaine anesthesia, as well as implementing strict exclusion criteria.

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The aims of this study were to (1) assess VE during uroflowmetry in healthy females randomized to receive high concentration intraurethral lidocaine or placebo, (2) assess whether high concentration intraurethral lidocaine changed pain during catheterization, and (3) confirm the pressure-flow changes reported by Kisby et al. We hypothesized that VE and catheterization pain would be lower in the group receiving high concentration lidocaine through disruption of sensory feedback from the urethra. By clarifying the reflex mechanisms that may underlie efficient bladder emptying, we hope to advance knowledge of the micturition reflex and enable novel treatments to improve symptoms and function.

MATERIALS AND METHODS

This was a randomized, double-blind, placebo-controlled trial of healthy adult female volunteers recruited at Duke University between October and December 2018. Approval for this study was obtained from the Duke University Health System Institutional Review Board and written informed consent was obtained from all participants. The trial was registered at clinicaltrials.gov (NCT03637582).

Prospective participants were recruited via electronic and print advertisements and were compensated for their time and travel. Participants underwent an initial phone screen followed by an in-office screen to determine eligibility. The in-office screen consisted of a review of demographics, health history, and medications and completion of the validated Lower Urinary Tract Symptoms (LUTS) Questionnaire.[10] Inclusion criteria were: (1) asymptomatic females ages 18-60, (2) able to provide informed consent and agree to the risks of the study, (3) willing to abstain from caffeine and alcohol for 24 hours, (4) willing to avoid taking anticholinergic medications (for reasons other than incontinence) for 1 week prior to the study, and (5) no health conditions as indicated in the exclusion criteria. Exclusion criteria were: (1) pelvic organ prolapse past the hymen, (2) neurologic condition (eg, Parkinson's disease, multiple sclerosis, myasthenia gravis, and stroke within the past 6 months), (3) bladder pain syndrome, (4) recurrent urinary tract infections, (5) body mass index >40, (6) positive pregnancy test at time of consent, (7) positive urine dip ($\geq$+1 nitrites or $\geq$+1 leukocyte esterase) and urinary tract infection symptoms, (8) $\geq$+1 blood on urine dip, and (9) >2 replies of $\geq$ "sometimes" on the LUTS questionnaire. Additionally, participants performed a baseline uninstrumented uroflowmetry after confirmation of at least 250 mL of urine in the bladder via a standard clinic transabdominal bladder scanner. Participants were asked to void in their usual fashion over a uroflowmetry load cell. The PVR was then assessed with a bladder scanner. Participants also completed the validated Visual Analog Scale (VAS) to determine baseline pain during voiding.[11] They were asked to place a hashmark on a 100 mm line to represent their degree of pain from "no pain" to "intolerable pain." Participants were excluded if they demonstrated an abnormal baseline uroflowmetry (eg, intermittent flow pattern, VE <80%) or VAS baseline scores >10 mm.

Following the in-office screen and determination of eligibility, participants were randomized to receive intraurethral administration of 2 doses of either 5 mL of plain aqueous gel (KY Jelly; Reckitt B enckiser, herein referred to as placebo) or 4% lidocaine gel (Alocane; Duke Investigational Drug Services, Durham, NC); each dose was separated by 15 minutes. MATLAB Version 9.4 (MathWorks Inc., Natick, MA) was used to create the randomization chart with the random permutation function (randperm) and a block of 4 trials (0/0/1/1) that was repeated 6 times to account for exclusions after randomization. The identically appearing study drug syringes were allocated into consecutively numbered opaque envelopes by an unmasked study coordinator who did not participate in study visits or analysis. Randomization envelopes were chosen consecutively by investigators performing the urodynamic studies (UDS). The study was double-blind, as participants and the research staff, aside from the unmasked coordinator, remained masked to study drug assignment for the duration of the study.

Prior to undergoing uroflowmetry with placebo or lidocaine gel, the participant's bladder was scanned to ensure at least 250 mL of urine was again present. If the participant had <250 mL, more time was allowed for physiological filling. Once adequate filling occurred, the randomly allocated study drug was administered. In the semirecumbent position, the participant's urethral meatus was cleansed with betadine, the urethra was cannulated with an 18-gauge vascath tip attached to the syringe, and 5 mL of the drug was slowly injected along the length of the urethra. The drug was left in place for 15 minutes with the participants in a semirecumbent position. The second dose was then administered similarly. The participant was asked once again to void in their usual fashion over a uroflowmetry load cell to obtain a second, post-drug uninstrumented uroflowmetry. A PVR was obtained both by bladder scanner and in and out catheterization. Twenty minutes was allocated between the first study drug administration and uroflowmetry and up to 60 minutes was allowed between the second study drug administration and end of study. The terminal half-life of lidocaine hydrochloride 2% is 90-120 minutes with 30-60 minutes duration of action.[12] We expect that our cohort should have received adequate urethral anesthesia for the duration of the urodynamic study.

To evaluate the impact of urethral anesthesia on additional urodynamic parameters, participants then completed complex cystometry and micturition pressure-flow studies. A dual-sensor 8-french catheter was inserted through the urethra into the bladder and an 8-french catheter was inserted into the vagina to measure intra-abdominal pressure. VAS was administered following catheter insertion to assess pain. Surface electromyography pads were placed at the 3 o'clock and 9 o'clock positions on the perineum to assess pelvic floor muscle recruitment during voiding. The catheters and leads were secured to the participant and the bladder was then filled with normal saline at room-temperature at 60 mL/min. Standardized questions were administered to obtain the following values: first sensation of filling, first desire to void, strong desire to void, and maximum cystometric capacity (MCC). Bladder pressure was continuously monitored for evidence of involuntary detrusor contractions or incontinence. The infusion pump was stopped at MCC. The micturition pressure-flow study was then performed by having the participant void into a beaker on the load cell with the pressure catheters in place. The following values were recorded: voided volume, detrusor and abdominal pressure, intermittent flow patterns, defined as a noncontinuous flow with repeated starts and stops (0 mL/s) during a void, and pelvic floor muscle activity, defined by the presence or absence of elevated electromyography tone during a void.[13] A final PVR was also obtained by in and out catheterization.

Based on the mean and standard deviation (92 ± 6.3%) from previous literature,[9] a power analysis of the 2-tailed *t* test with baseline VE from uroflowmetry determined that a sample size of 10 per group enabled detection of a 30% decrease in VE with a power (1-β) of 1.0 (G*Power 3.1.9.2). We defined VE as voided volume/(voided volume + PVR) and determined a reduction of 30% to be clinically relevant by expert opinion (CLA). Greater than 30% reduction in VE was achieved in previous animal studies using intraurethral lidocaine.[5] Additionally, prior studies in women with voiding disorders, including detrusor underactivity, detrusor hyperactivity with impaired contractility, and bladder outlet dysfunction, exhibited voiding efficiencies from 31.0 ± 33.2% to 62.6 ± 32.3%.[14] If reduced urethral sensory feedback contributes to impaired bladder emptying in these patients, it is therefore reasonable to expect a 30% decrease in VE from control after intraurethral lidocaine. Statistical analyses were performed with IBM SPSS Version 25 (Armonk, NY) and GraphPad Prism Version 8 (San Diego, CA). All analyses were conducted while the investigators remained blinded to which of the 2 groups constituted those receiving intraurethral lidocaine and controls. Continuous variables with normal distribution were analyzed by Student's *t* test or Welch's *t* test after group variance was tested using Levene's test. To classify placebo and lidocaine groups in uroflowmetry, a logistic regression analysis was performed with backward stepwise selection based on the likelihood-ratio statistic. Complex cystometry repeated measures data were analyzed by a linear mixed-effects model. Continuous variables with non-normal distribution were analyzed by Mann-Whitney *U* test, and categorical variables were analyzed by Fisher's exact test. *P* values ≤.05 were considered statistically significant.

RESULTS

Thirty women were recruited and 23 provided informed consent (Fig. 1). Two participants failed the LUTS questionnaire (>2 replies of "sometimes"), and 3 participants demonstrated abnormal baseline uroflowmetry; these participants were excluded prior to randomization (Fig. 1). The final population for data analysis included 18 participants randomized to receive placebo ($n = 10$) or lidocaine ($n = 8$) (Fig. 1). The mean age was 31 years and mean body mass index was 25 kg/m^2 (Table 1). Participants were 61% Caucasian, 17% Black, 6% Asian, and 17% other (Table 1). Eight of the participants had at least 1 prior vaginal delivery, and all but 1 participant were premenopausal (Table 1).

Uroflowmetry: Baseline uroflowmetry VE was similar between the placebo and lidocaine groups (88 ± 6.6% vs 91 ± 5.8%, $P = .33$). Changes in VE (post drug − baseline) after study drug administration were similar between placebo and lidocaine groups (−5.4 ± 14% vs 1.7 ± 6.4%, $P = .21$, Fig. 2A). Backward stepwise elimination in the logistic regression analysis identified voided volume and average flow rate to predict the probability that participants received lidocaine. The final model performed significantly better than with only the intercept ($P = .024$) and was able to classify correctly 90% of those receiving placebo and 87.5% of those receiving lidocaine (Fig. 2B). The model revealed that for every unit increase in voided volume, the odds of receiving

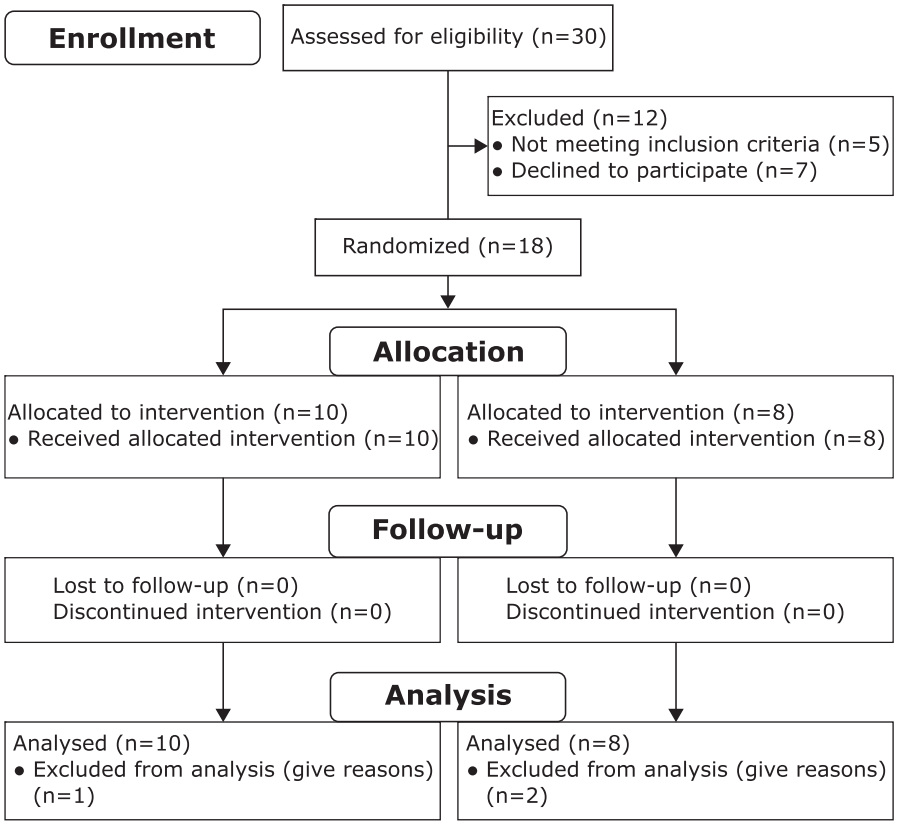

Figure 1. CONSORT flow diagram. Flow diagram including enrollment, intervention allocation, follow-up, and data analysis. $n = 1$ excluded from the pressure flow study analysis of the placebo group due to an inability to void, and $n = 2$ excluded from the cystometry analysis of the lidocaine group due to issues with the infusion catheter.

Table 1. Baseline demographics

Variable	Placebo ($n = 10$)	Lidocaine ($n = 8$)
Age (y)	32 ± 10	30 ± 5
Race		
White	7 (70)	4 (50)
Black	2 (20)	1 (12.5)
Asian	0 (0)	1 (12.5)
Other	1 (10)	2 (25)
BMI (kg/m^2)	26 ± 6.9	24 ± 4.2
Education		
High school	1 (10)	0 (0)
College graduate	3 (30)	4 (50)
Graduate/professional	6 (60)	4 (50)
Mode of delivery		
Vaginal delivery	5 (50)	3 (37.5)
Cesarean section	1 (10)	1 (12.5)
Menopausal status		
Premenopausal	9 (90)	8 (100)
Postmenopausal	1 (10)	0 (0)
Smoker	0 (0)	0 (0)
Pelvic organ prolapse	0 (0)	0 (0)
ARS Score	0	0
FCI	0.5 (0, 1.25)	0 (0, 0)
LUTS score	5 ± 4	4 ± 3

ARS, anticholinergic risk scale; BMI, body mass index; FCI, functional comorbidity index; LUTS, lower urinary tract symptom; POP, pelvic organ prolapse.
Data are presented as mean ± standard deviation, median (25%, 75% quartile), or *n* (%).

lidocaine increased by 1.012 ($P = .04$). In addition, the lidocaine group exhibited lower average flow rates per voided volume (0.04 ± 0.02 s^{-1} vs 0.02 ± 0.01 s^{-1}, $P = .04$, Fig. 2C).

Complex Cystometry: Urinary bladder sensation, including first sensation of bladder filling (57 ± 50 mL vs 78 ± 56 mL), first desire to void (121 ± 70 mL vs 158 ± 77 mL), strong desire to void (299 ± 147 mL vs 261 ± 97 mL), and MCC (411 ± 197 mL vs 359 ± 104 mL) during cystometric filling were similar between placebo and lidocaine groups ($P = 0.76$). Data were missing for complex cystometry of 2 participants in the lidocaine group due to issues with the infusion catheter.

Pressure-Flow Studies: There were no significant differences between placebo and lidocaine groups during micturition pressure-flow studies including VE ($P = .81$), increased abdominal recruitment ($P = 1.0$), pelvic floor muscle activity ($P = .59$), or intermittent flow patterns ($P = .62$) (Table 2). Data were missing for the micturition pressure-flow studies of 1 participant in the placebo group due to an inability to void.

Visual Analog Scale: Baseline VAS scores were similar between placebo and lidocaine groups (0 [0, 1.25] mm vs. 0 [0, 0] mm, $P = .43$). After catheterization, VAS scores remained unchanged (26.7 ± 12.8 mm vs 36.9 ± 26.8 mm, $P = .34$), however participants with lidocaine demonstrated greater variability in their responses ($P = .003$).

COMMENT

In this randomized, double-blind, placebo-controlled trial, we determined that intraurethral 4% lidocaine did not decrease VE or VAS scores following catheterization. Despite the lack of change in these outcomes, we were able to classify correctly participants receiving lidocaine based on uroflowmetry voided volume and average flow rate. The lidocaine group also exhibited lower average flow rates per voided volume. These results suggest that while participants can empty their bladder efficiently, urethral sensory feedback may still be having an underlying role in regulating urinary flow and output.

A detrusor contraction during micturition is believed to be maintained by positive feedback from urethral sensory receptors as urine flows through the urethra and engages the augmenting reflex. Evidence for this hypothesis arose from a study in rats where intraurethral infusion of 2% lidocaine decreased detrusor contraction amplitude and duration and decreased VE.[5] However, few studies have evaluated the reflex in humans. Shafik et al examined the effect of intraurethral anesthesia on micturition in males and females using 5% xylocaine gel.[8] They found increased strain-voiding in the form of elevated vesical pressure as well as elevated PVR after voiding in the xylocaine group.[8] VE was not examined in their study. Kisby et al quantified the effect of 2% intraurethral lidocaine on VE and other urodynamic parameters in healthy females.[9] They did not observe a significant difference in VE between groups, however, the lidocaine group had elevated pelvic floor muscle activity and interrupted urinary flow streams.[9] The findings in these studies suggest that participants who receive intraurethral anesthesia require more effort to empty their bladder.

In the current study of healthy females, we administered 2 doses of 4% lidocaine gel with 15 minutes between doses intended to produce a greater urethral anesthetic effect than in the Kisby et al study.[9] Additionally, we excluded participants with an abnormal baseline uroflowmetry or reported pain on baseline VAS to obtain participants with no potential underlying urinary issues. Our primary outcome was VE, as this is a clinically relevant and easy to measure clinical parameter. Although there was no difference in VE between groups, the average flow rate per voided volume was lower in the lidocaine group, indicating that those who received intraurethral anesthesia required more time to void the same volume as those who received placebo. This may suggest a blunting effect of the anesthetic on urethral sensory feedback, reducing the feedback of excitatory signals to the bladder but not impacting overall VE. While we cannot exclude lidocaine entering the bladder during dwell time in a semirecumbent position, the lack of functional effects on bladder sensation during cystometry suggest minimal off target penetration to the bladder.

Unlike Kisby et al, our study did not demonstrate differences in abdominal recruitment, pelvic floor muscle activity, or intermittent flow patterns during pressure-flow studies. This may be because we excluded those with abnormal baseline uroflow studies. Additionally, it is possible that in a population with healthy bladder function, any disruption to the augmenting reflex could be overcome thereby maintaining adequate VE. To assess further changes in voiding function with intraurethral anesthesia,

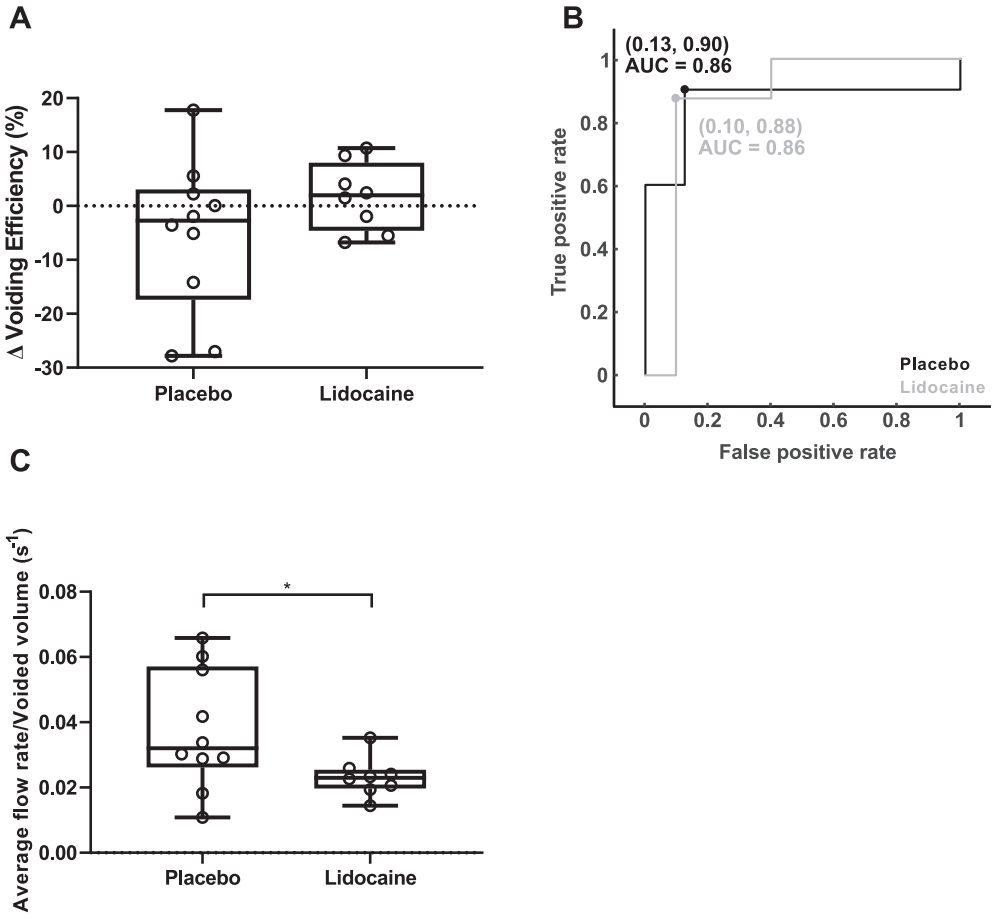

Figure 2. Uroflowmetry voiding parameters with placebo or lidocaine. (**A**) Intraurethral 4% lidocaine did not change uroflowmetry voiding efficiency (delta of post drug − baseline). (**B**) Receiver operating characteristic (ROC) curves demonstrating the correct classification of 90% of those receiving placebo and 87.5% of those receiving lidocaine with a ROC-AUC of 0.86. (**C**) Intraurethral 4% lidocaine exhibited lower average flow rates per voided volume in uroflowmetry. $n = 8$-10, $^*P = 0.04$ with Welch's t test (Levene's test for equality of variance, $P = 0.008$).

future studies may be performed where participants undergo UDS in each study condition on different days; this could reduce confounding factors, however, we would not expect reduced urethral sensation to have significant effects on the VE of healthy participants. Further studies may also be performed to evaluate the effect of intraurethral anesthesia in symptomatic women to assess whether disruption of sensory feedback worsens voiding dysfunction. Alternate ways to disrupt the augmenting reflex could be explored, and may include a different anesthetic agent, administration technique, or other types of nerve block.

Table 2. Micturition pressure-flow study parameters with placebo or lidocaine

Variable	Placebo ($n = 9$)	Lidocaine ($n = 8$)	P*
Voiding efficiency (%)	92 (75, 95)	93 (91, 94)	.81
PVR (mL)	60 (37, 199.5)	51 (32, 72.25)	.42
Pdet@Qmax (cmH_2O)	44 ± 15	40 ± 15	.64
Pabd recruitment during flow	1 (11)	1 (12.5)	1.00
Intermittent flow pattern	4 (44)	2 (25)	.62
Elevated EMG activity	3 (33)	1 (12.5)	.59

EMG, electromyography; Pabd, abdominal pressure; Pdet@Qmax, detrusor pressure at maximum flow rate; PVR, post void residual.
Data are presented as mean ± standard deviation, median (25%, 75% quartile), or n (%).
Intraurethral 4% lidocaine did not change voiding efficiency or other micturition pressure-flow study variables.
* Analyzed by Student's t test, Mann-Whitney U test, or Fisher's exact test where appropriate.

Prior studies demonstrated varying degrees of pain reduction with catheterization and intraurethral anesthesia.[9,15-17] Kisby et al did not find a clinically significant difference in VAS pain scores with 2% intraurethral lidocaine gel following catheterization.[9] However, Chan et al did report a clinically significant difference in pain with the use of 2% lignocaine gel.[17] Our study using 4% lidocaine gel did not show a difference in VAS pain scores following catheterization, however participants receiving lidocaine demonstrated greater variability in their responses. To administer 4% lidocaine in the present study, a vascath tip attached to a luer lock syringe was used. The tip was inserted into the urethra, and gel was administered along the length of the urethra. Perhaps the lidocaine was effective in reducing pain for some of the participants in our study, but the administration

or catheterization technique increased pain scores in others. Future studies may investigate alternate methods of administering anesthesia to evaluate for differences in pain scores. As previously suggested, participants could also undergo UDS in each study condition on different days to assess VAS pain scores within participants.

Inefficient voiding may result in incomplete bladder emptying and urinary retention, which decrease quality of life and increase healthcare utilization.[10,18] For most patients suffering from urinary retention, there is concern for developing complications including overflow incontinence, hydronephrosis, infection, or renal failure.[19] Management options for women with urinary retention are limited and mostly include intermittent or indwelling catheterization, urethral dilation, reconstructive surgery, or, in certain cases, sacral neuromodulation.[20] To treat the underlying pathophysiology, we must better understand the mechanisms that enable efficient voiding in healthy humans and determine if the augmenting reflex is a potential target for treatment, especially neuromodulation.[21] Additionally, pharmacologic targets that augment sensory input to the augmenting reflex may be effective in increasing bladder contractility.[22]

CONCLUSION

We found that intraurethral 4% lidocaine does not decrease VE. Our work corroborates other researchers' findings that urethral sensory feedback may have a role in regulating urinary flow and output during human micturition. In addition, intraurethral 4% lidocaine does not alter VAS pain scores following catheterization. We would therefore not recommend intraurethral lidocaine prior to or during routine UDS of healthy women as it may impact the diagnostic results without reducing pain.

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